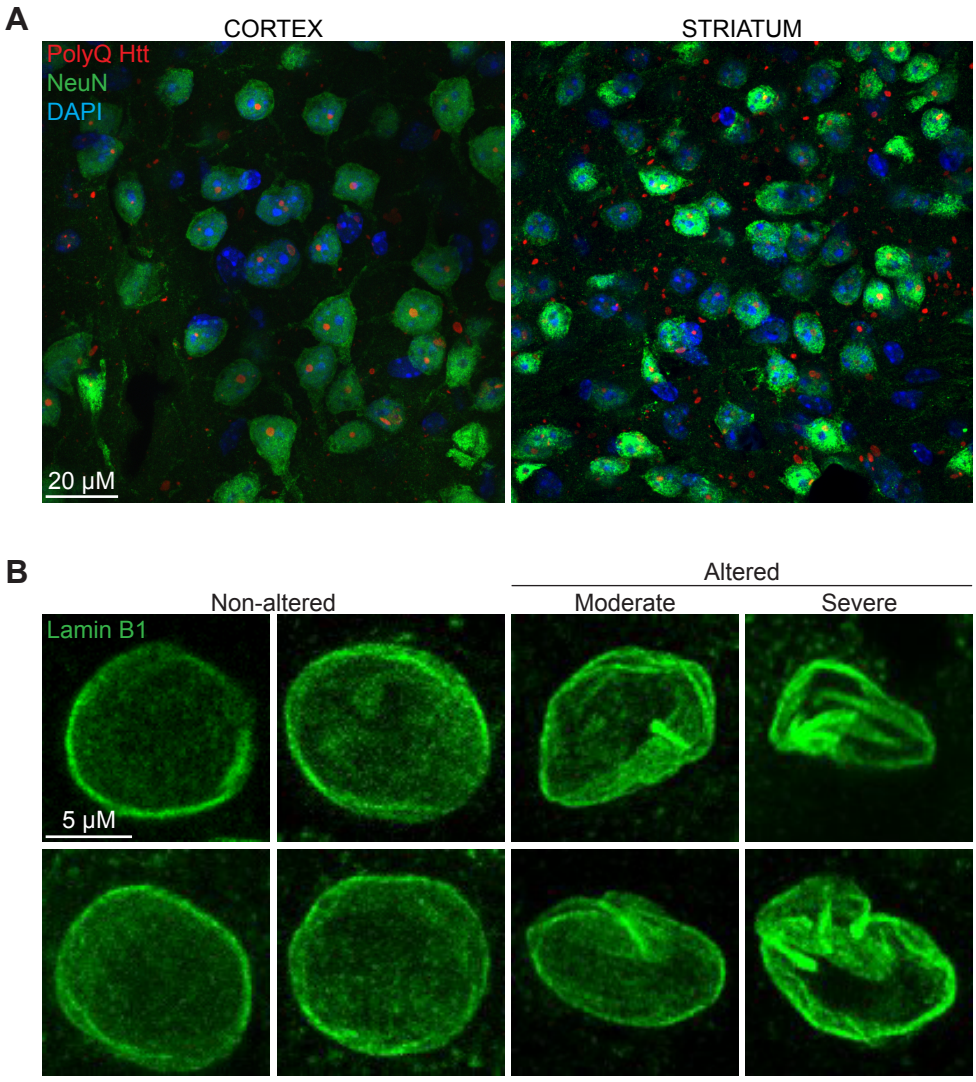

Figure S1. Related to Figure 1. Disrupted nuclear envelope in cortex and striatum of mice expressing mutant Huntingtin
(A) Immunofluorescence (IF) of NeuN (green) and polyQ Htt (red) in cortical and striatal sections of 18-month $Htt^{Q175/Q175}$ mice. **(B)** Distinct nuclear envelope morphologies revealed by IF of lamin B1 in mouse brain.

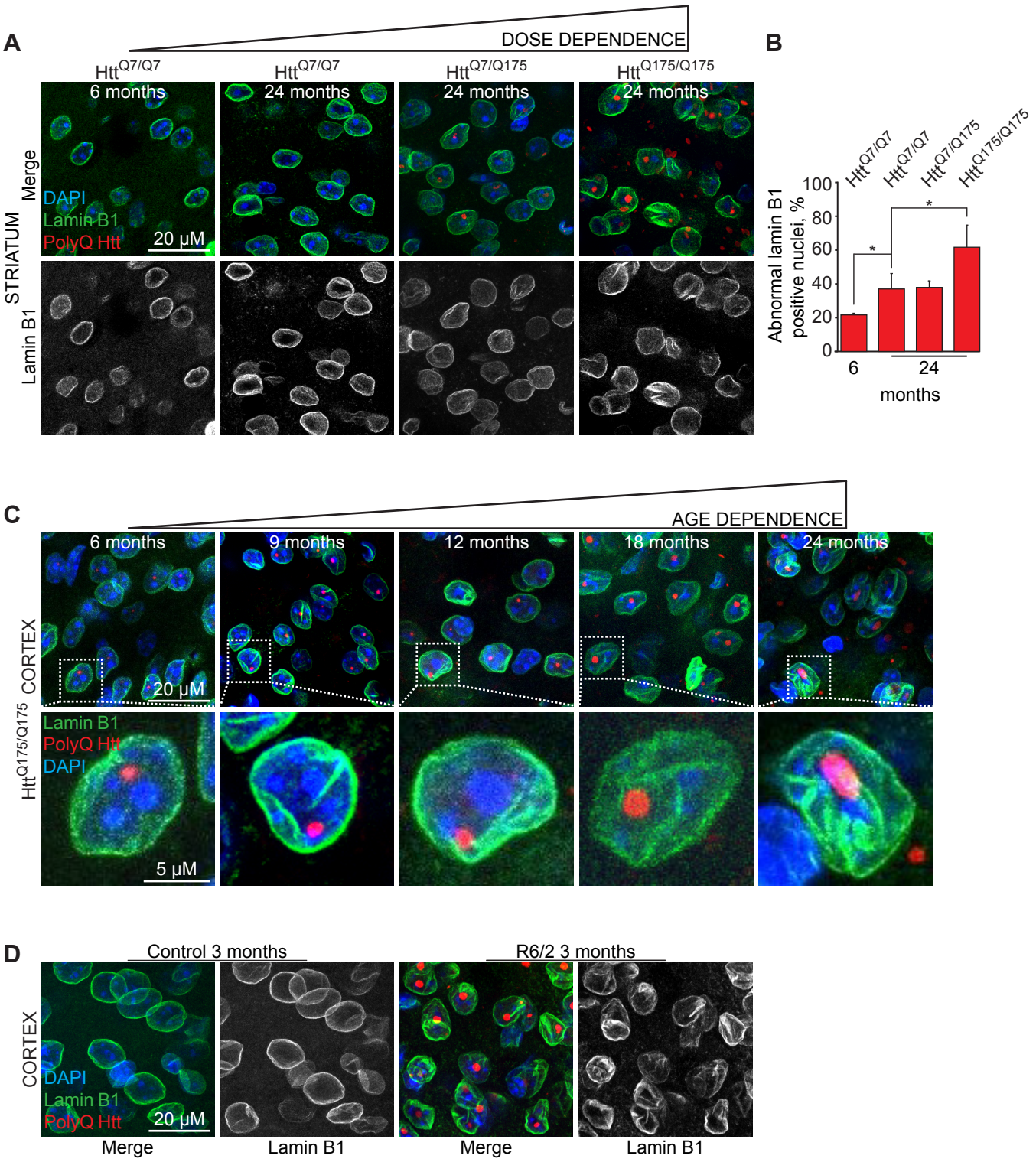

Figure S2. Related to Figure 1. Disrupted nuclear envelope in cortex and striatum of mice expressing mutant Huntingtin
(A) Immunofluorescence (IF) of lamin B1 (green) and polyQ Htt (red) in striatum of mice of indicated ages expressing one ($Htt^{Q7/Q175}$) or two ($Htt^{Q175/Q175}$) copies of expanded polyQ Htt and wild type littermates ($Htt^{Q7/Q7}$). **(B)** Percentage of altered nuclear envelopes in striatum of mice shown in **(A)**. Data are shown as mean ± SEM. *: P<0.05 chi-square test. 300-700 nuclei were counted per genotype and age. **(C)** IF of lamin B1 (green) and polyQ Htt (red) in cortex of aging $Htt^{Q175/Q175}$ mice. **(D)** IF of lamin B1 (green) and polyQ Htt (red) in cortex of 3 month-old control and R6/2 mice. **A**, **C**, **D**: nuclei were stained with DAPI. Z projections of 30 consecutive slices (3 μM) are shown.

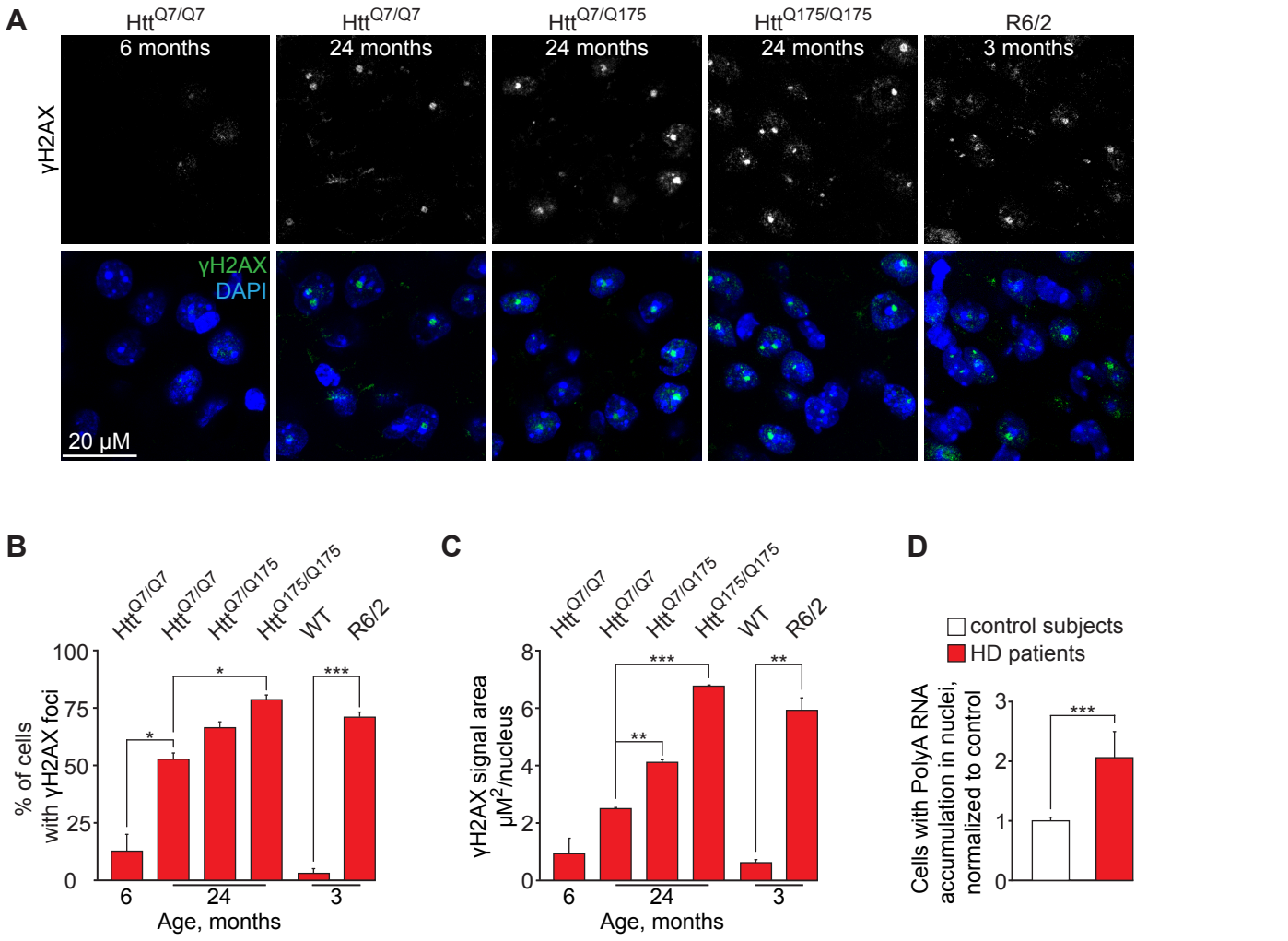

Figure S3. Related to Figures 1 and 2.
Expanded polyQ Huntingtin induces DNA damage and mRNA accumulation in nuclei
(A-C) Immunofluorescence of γH2AX **(A)** and percentage of cells with γH2AX foci **(B)** and area of γH2AX signal per nucleus **(C)** in cortical sections of mice of indicated genotypes and ages. Data are presented as mean ± SEM. *: P<0.05, **: P<0.01, ***: P<0.001, unpaired t test. 100-200 cells per animal were counted. Nuclei were stained with DAPI.
(D) Quantification of cells with mRNA accumulation in nuclei of two non-neurological disease control subjects and two Huntington's disease patients, normalized to control. At least 70 nuclei were counted per each group. Data are presented as mean ± SEM. ***: P<0.001, chi-square test.

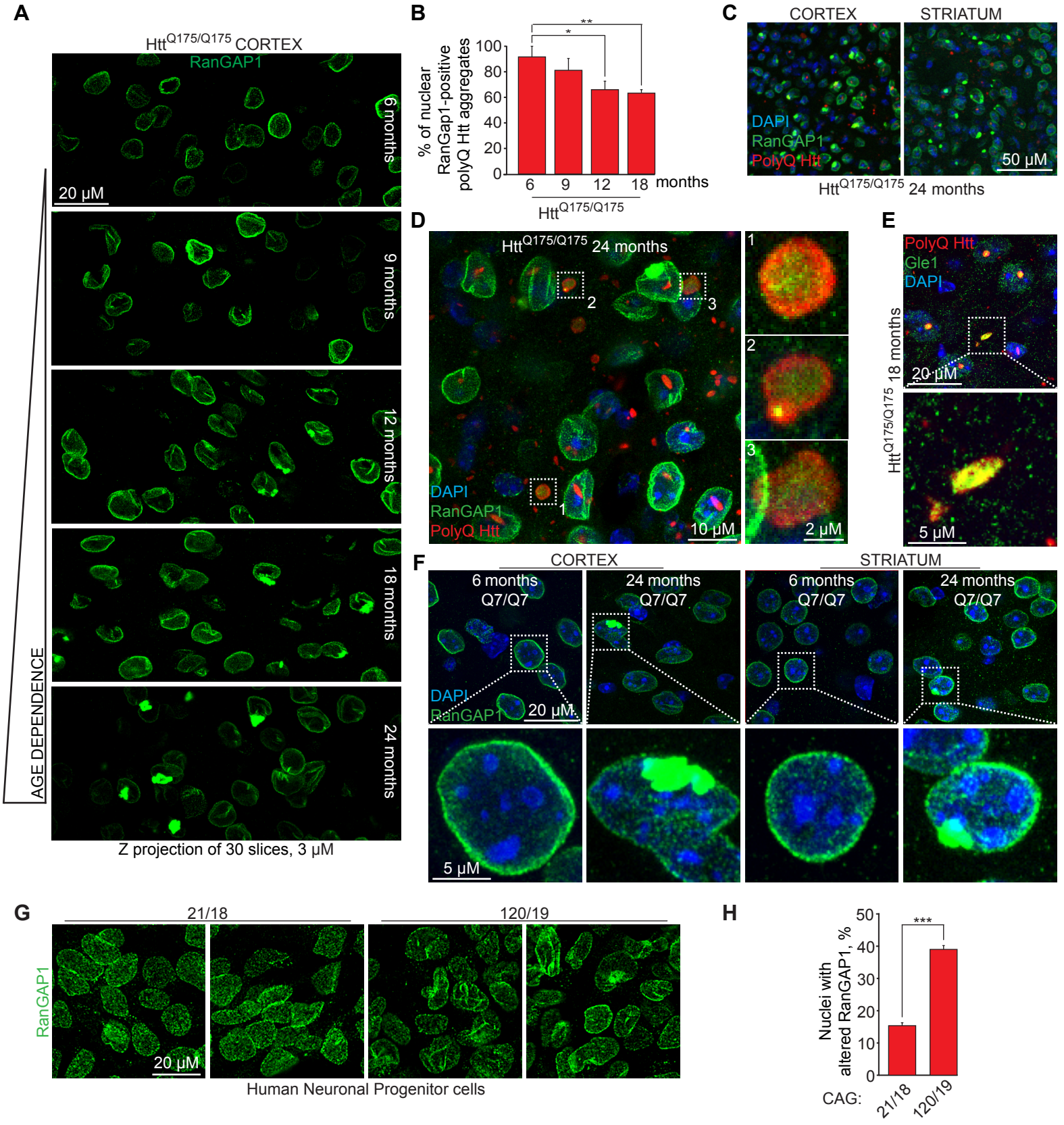

Figure S4. Related to Figures 3 and 4. Expanded polyQ Huntingtin sequesters RanGAP1 and Gle1

(A) Immunofluorescence (IF) of RanGAP1 in cortical sections of Htt$^{Q175/Q175}$ mice of indicated ages. **(B)** Percentage of nuclear polyQ aggregates, positive for RanGAP1, in mice of indicated genotypes and ages. Data are shown as mean ± SEM. *:P<0.05, **:P<0.01, chi-square test. At least 100 cells were analyzed for each genotype and age. **(C)** IF of RanGAP1 (green) and polyQ Htt (red) in cortex and striatum of 24 month-old Htt$^{Q175/Q175}$ mice. Z projections of 10 consecutive slices (15 μM) are shown. **(D)** IF of RanGAP1 (green) and polyQ Htt (red) in cortex of 24 month-old Htt$^{Q175/Q175}$ mice. Z projections of 30 consecutive slices (3 μM) are shown. **(E)** IF of Gle1 (green) and polyQ Htt (red) in cortex of 18 month-old Htt$^{Q175/Q175}$ mice. **(F)** IF of RanGAP1 (green) in cortex and striatum of wild-type Htt$^{Q7/Q7}$ mice of indicated ages. Z projections of 30 consecutive slices (3 μM) are shown. **C-F**: Nuclei were stained with DAPI. **(G, H)** IF of RanGAP1 **(G)** and percentage of nuclei with altered RanGAP1 staining **(H)** in human neuronal progenitor cells with indicated number of CAG repeats. Data are shown as mean ± SEM. ***:P<0.001, chi-square test. At least 5000 cells were analyzed for each genotype.

Table S1. Related to Figures 1E and 4SG. iPSC-derived neuronal progenitors

Coriell Number	iPS Clone ID	iPS CAG (longer)	iPS CAG (shorter)	Age at Sampling	Gender	iPS Reference	Figure
GM05400	CS00iCTR21-n1	21	18	6 years	Male	HD iPSC Consortium 2017	Fig 1E, F, S4G, H
ND39258	CS09iHD109-n4	120	19	9 years	Female	HD iPSC Consortium 2017	Fig 1E, F, S4G, H

Table S2. Related to Figures 1G, H, 2C, S3D and 4E, F. Autopsy samples from Huntington's disease patients and control individuals

Bank of origin	Age at autopsy	Gender	Hours Post-mortem	CAG	Diagnosis	Figure
UCSD	37	Male	ND	50/15	HD	Fig4E, F
UCSD	35	Female	14	61/17	HD	Fig4E, F
UCSD	54	Female	ND	47/21	HD	Fig4E, F
UCSD	48	Female	ND	47/23	HD	Fig4E, F
MGH	63	Male	5	ND	HD	Fig1G, H, 4E, F
MGH	21	Male	7	ND	HD	Fig2C, S3D, 4E, F
MGH	33	Male	13	ND	HD	Fig1G, H, 2C, 4E, F S3D
UCSD	40	Male	ND	ND	Control	Fig4E, F
UCSD	80	Female	12	ND	Control	Fig2C, S3D
UCSD	93	Female	18	ND	Control	Fig4E
MGH	92	Male	ND	ND	Control	Fig1G, H, 4E, F
MGH	47	Male	3	ND	Control	Fig1G, H, 2C, 4E, F, S3D